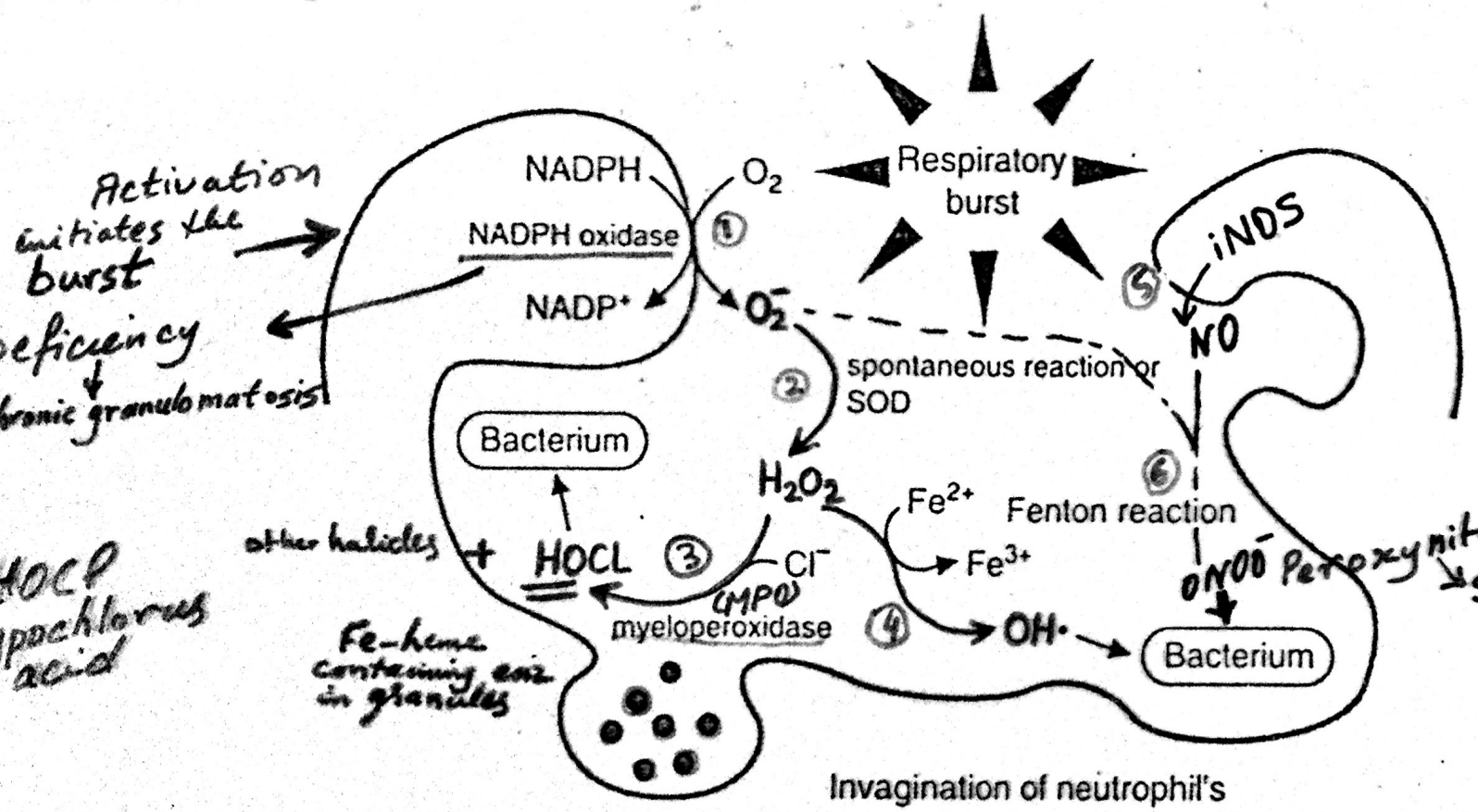
Production of reactive Oxygen species during the phagocytic Respiratory burst by activated macrophages, neutrophils & eosinophils.



Activation initiates the burst

eficiency
↓
hronic granulomatosis

HOCl - hypochlorous acid
powerful toxin - halogenation and ox$^{n}_{\cdots}$.
e.g. Fe- & SH- centers
ox. decarboxylation,
ox. deamination
breaking peptide bonds

HOCl
ypochlorous acid

Peroxynitrite → generate RNOS

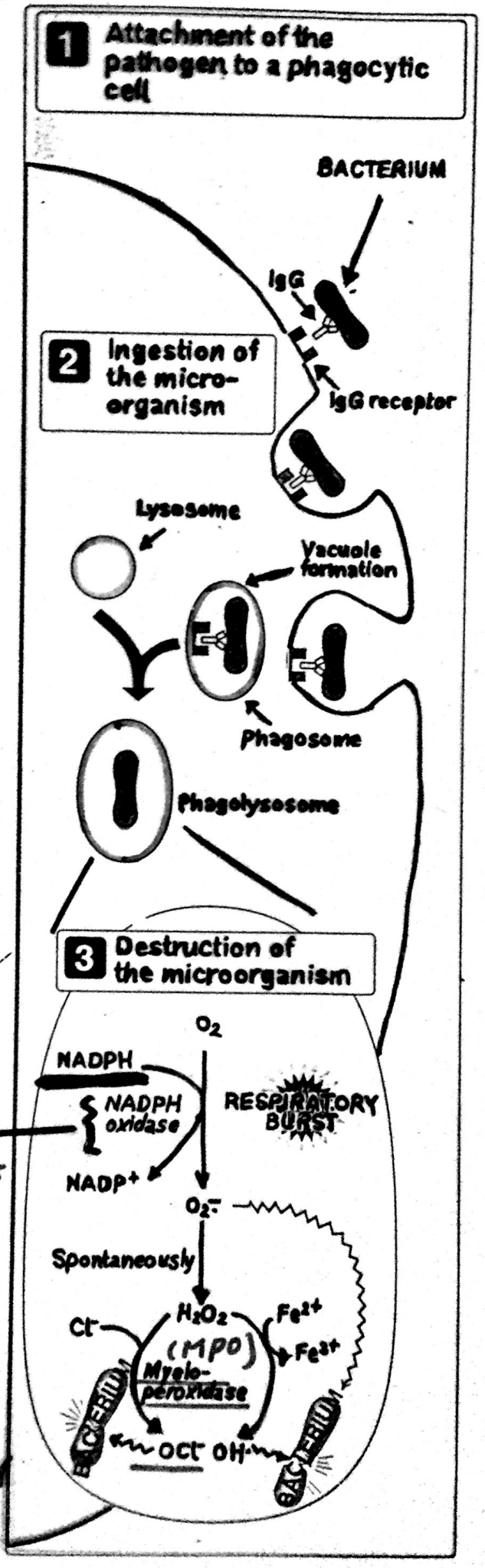
OH· & HOCl attacks bacterial cells → lysis

30-60 min
Consumption of O_2 } ← Respiratory Burst

$ONOO^-$ Peroxynitrite
↓ H^+ physiologic pH
Peroxynitrous acid
$HONO_2$
NO_3^- safe
NO_2^+ nitronium ion (nitration agent)
OH· free radicals
NO_2·

D-Phagocytosis by white blood cells

Uses NADPH



Deficiency

Chronic granulomatosis

MPO-lysosomal enz.

HOCl hypochlorous acid

NO and RNOS

- NO is a free radical . diffuses readily.
- Essential to life and toxic
- Neurotransmitter , vasodilator
  Prevents platelet aggregation | at low concentration

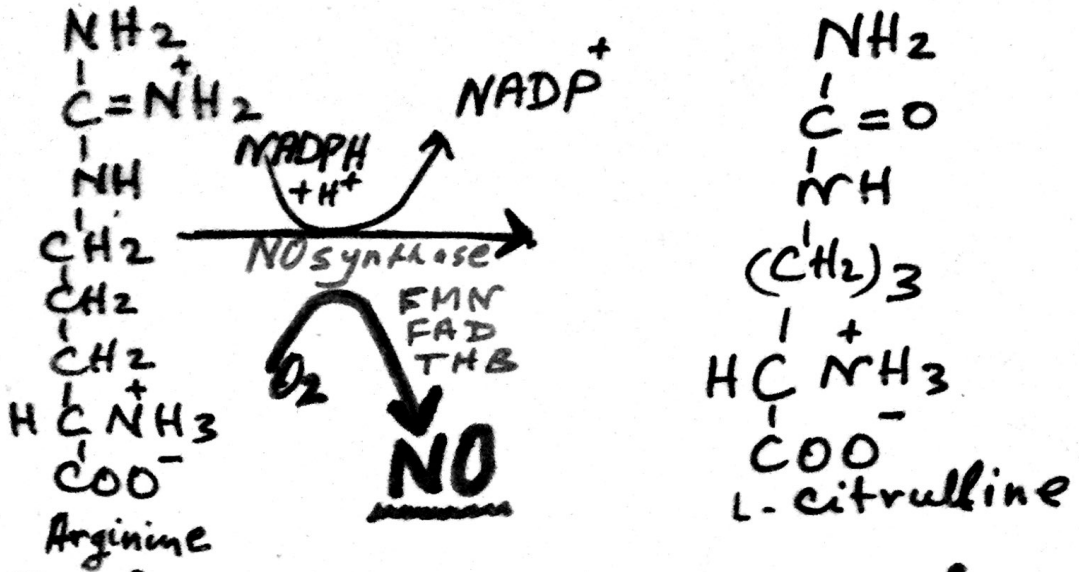
- At high concentration combines with $O_2^{\cdot}$ or O_2 to form RNOS
  RNOS are involved in neurodegenerative diseases and inflammatory diseases

NO Synthase
- nNOS - Isoform I (neural)
- eNOS - Isoform III (endothelium)

Both are constitutive enz. produce small amount of NO as neurotransmitter + hormone
- iNOS - Isoform II (inducible)

Induction of transcription in many cells of immune system → large amount of NO
↑NO → RNOS to kill invading bacteria

Synthesis of Nitric Oxide (NO)



- Relaxes smoth muscle

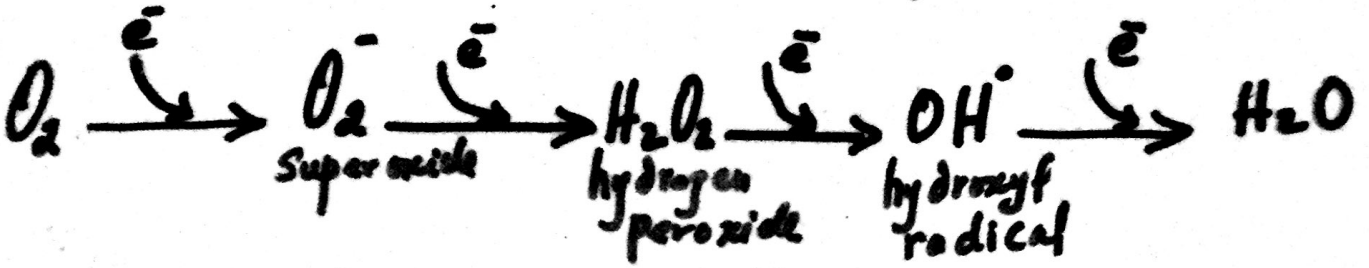
- $GTP \xrightarrow[NO(+)]{Cyclase} cGMP$
- cGMP activates PKG
- PKG phosphorylates Ca^{2+} protein channels which decrease Ca^{2+} entry to muscle cells which decrease Ca-calmodulin of myosin light chain kinase ↓ Therefore decreasing muscle contraction and favoring relaxation of vascular smooth muscle

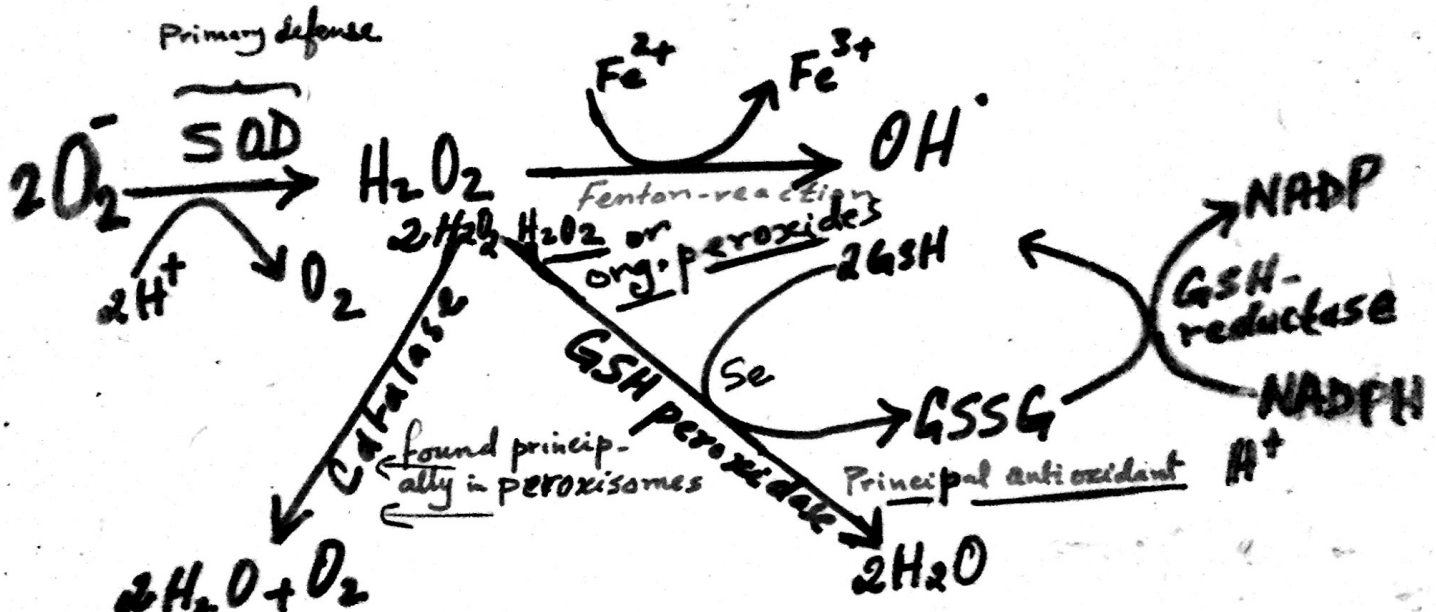
- Prevents platelet aggregation
- Neurotransmitter in brain
- Mediates tumoricidal and bactericidal actions of macrophages

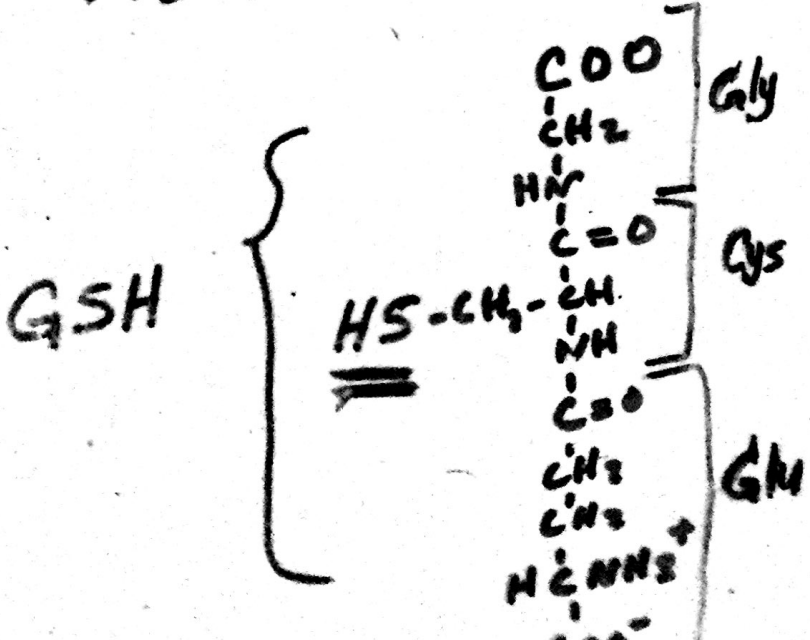
Cellular Defence Against O_2 toxicity:-

- Primary Antioxidants- Antioxidant Enzymes

SOD ; Catalase, GSH peroxidase, GSH reductase. Highest conc. in liver, adrenal & kidney (high content of peroxisomal & mit.)



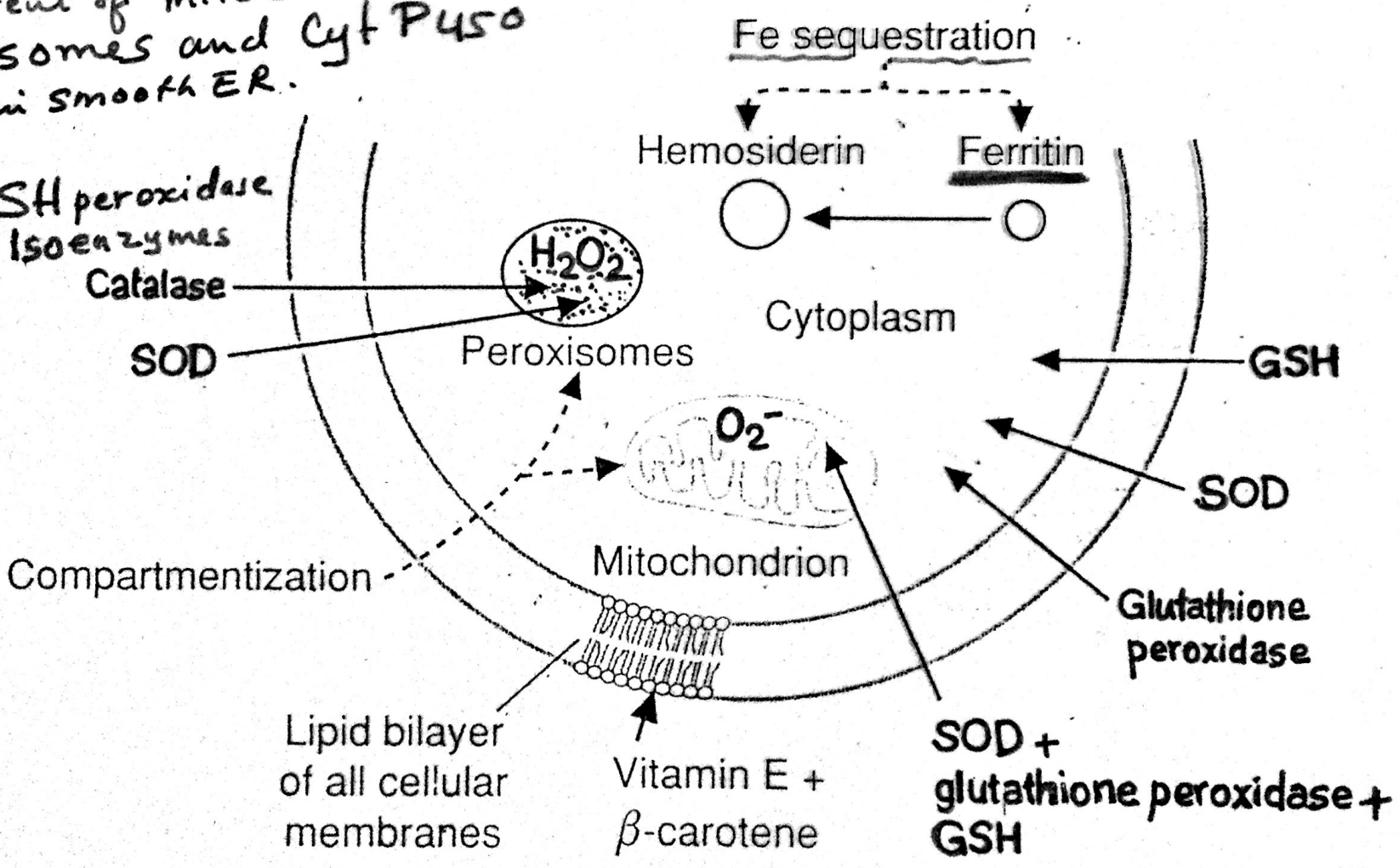




$GSH + GSH \xrightarrow{\text{Peroxidase}} GSSG$

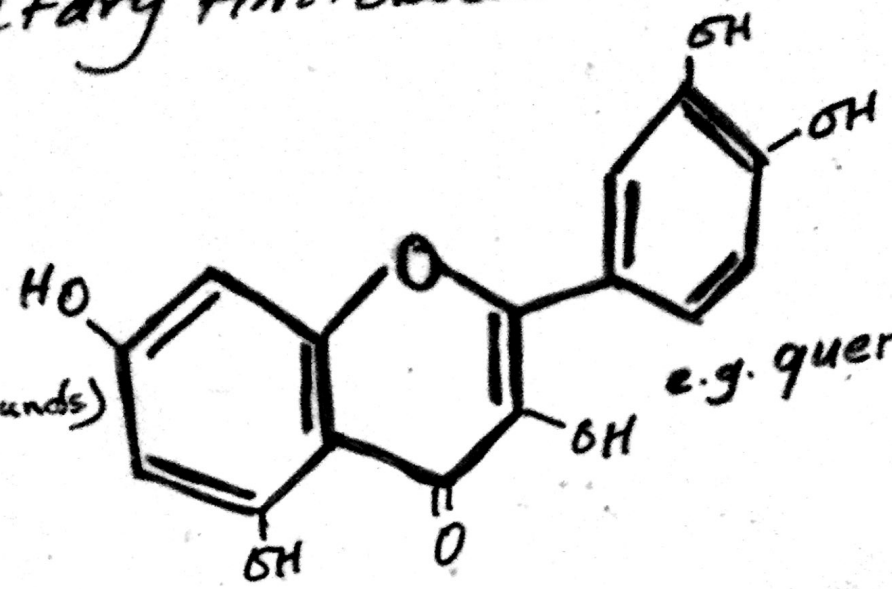
Compartmentization of free-radical defenses

- Highest activities are in liver, adrenal gland + kidney
- ↑ high content of mitochondria, peroxisomes and Cyt P450 enzymes in smooth ER.
- SOD and GSH peroxidase are present as isoenzymes



Other Dietary Antioxidants

Flavonoids
(Polyphenolic compounds)



e.g. quercetin

- green-tea
- Choclate
- red wine
- fruits skin, veg. (e.g. onion)

Possible functions:
- inhibition of O_2^- production e.g. X.O.↓ (xanthine oxidase)
- free radical scavenger
- chelate Fe + Cu
- maintenance of Vit E

Endogenous Antioxidants

- Uric acid
- GSH
- melatonin
- Bilirubin
- Lipoic acid
- Ubiquinone (Co Q10)

Some flavenoids:
- Catechins:- strawberries, green + black tea
- Kaempferol:- brussel sprouts + apple
- quercetin:- beans, onions, apples and fruit. sk
- Epicatechin:- Cocoa, red wine

- Secondary Antioxidants

A. Dietary :-

(1) Vitamins

Vitamin E (tocopherol)

Vitamin C

β-carotenes

(2) other dietary antioxidants

B. Endogenous antioxidants

C. Repair Mechanism of DNA, oxidized fatty acids & membrane lipids and oxidized amino acids

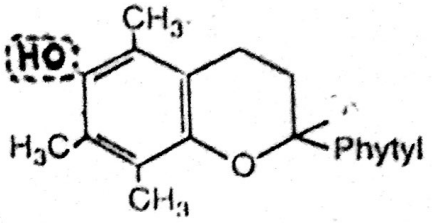
D. Compartmentation

e.g. peroxisomes, ferritin for Fe^{2+}

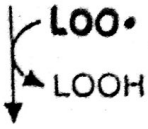
--- etc.

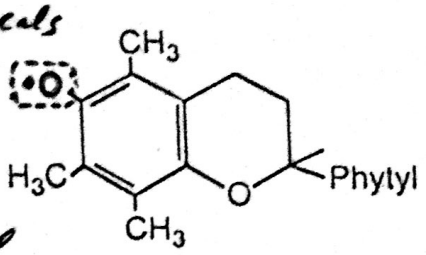
Vitamin Antioxidants:-

- Chain-breaking antioxidants.
Terminates free radical lipid peroxidation by:-
- Vit. E donate single e
- Carotenoids accept e from lipid peroxy radicals
- Vit C accepts single e from O_2^-, H_2O_2, $^1H^+$, HOCl & peroxyl radicals
- Vit C regenerate the reduced form of Vit. E

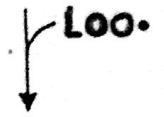


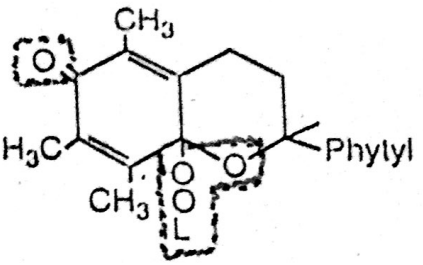
α-Tocopherol

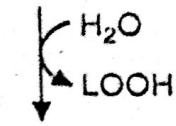


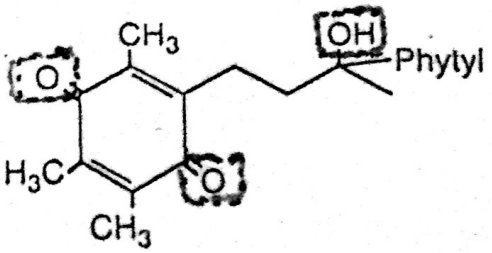


Tocopheryl radical









Tocopheryl quinone

Fig. 21.15. Vitamin E. Vitamin E terminates free radical lipid peroxidation by donating single electrons to form the stable, fully oxidized tocopheryl quinone. Of the eight or more different tocopherols that comprise vitamin E, α-tocopherol, shown here, is the most common in the diet.

Vit. E : most widely distributed antioxidant

- sole physiological role is to quench free radical reactions